Answer 1:

Bibliographic Information

Combining Agents that Target the Tumor Microenvironment Improves the Efficacy of Anticancer Therapy. Blansfield, Joseph A.; Caragacianu, Diana; Alexander, H. Richard, III; Tangrea, Michael A.; Morita, Shane Y.; Lorang, Dominique; Schafer, Peter; Muller, George; Stirling, David; Royal, Richard E.; Libutti, Steven K. Tumor Angiogenesis Section, Surgery Branch, National Cancer Institute, NIH, Bethesda, MD, USA. Clinical Cancer Research (2008), 14(1), 270-280. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:552920 AN 2008:8763 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Over the past 60 years, cytotoxic chemotherapy has targeted the cancer cell. Despite this, there have been few cancer cures. A new approach to cancer therapy is to target the multicellular biol. entity of the tumor microenvironment. Exptl. Design: Lenalidomide, an immunomodulatory drug, sunitinib, a tyrosine kinase inhibitor, and low-dose metronomic cyclophosphamide, were tested alone and in combination for their abilities to inhibit endothelial cell tube formation, rat aortic ring outgrowth, tumor growth, and metastatic development in mice. In addn., ectopic tumor lysates were evaluated for the presence of proangiogenic proteins. RESULTS: The three agents alone were shown to significantly inhibit endothelial cells' ability to form tubes and significantly inhibit the multicellular microenvironment in the rat aortic ring assay ($P < 0.01$ and $P < 0.001$). This effect was also significantly augmented when the agents were combined. Furthermore, the three-drug combination was able halt the progression of tumor growth almost completely in xenograft models of ocular melanoma, colon cancer, pancreatic cancer, and cutaneous melanoma. These agents significantly decrease the no. of proliferating cells in tumors, significantly increase the no. of cells undergoing active cell death in tumors, and significantly decrease the no. of blood vessels in treated tumors ($P < 0.05$). Combination therapy shows a decrease in the compensatory up-regulation of proangiogenic proteins after treatment when compared with single-agent therapy. CONCLUSIONS: This combination of agents causes an inhospitable microenvironment for tumor cells and shows great promise for use in the clinic.

Answer 2:

Bibliographic Information

Combination therapy targeting the tumor microenvironment is effective in a model of human ocular melanoma. Mangiameli, David P.; Blansfield, Joseph A.; Kachala, Stephan; Lorang, Dominique; Schafer, Peter H.; Muller, George W.; Stirling, David I.; Libutti, Steven K. Tumor Angiogenesis Section, Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. Journal of Translational Medicine (2007), 5 No pp. given. Publisher: BioMed Central Ltd., CODEN: JTMOBV ISSN: 1479-5876. http://www.translational-medicine.com/content/pdf/1479-5876-5-38.pdf Journal; Online Computer File written in English. CAN 148:45249 AN 2007:936469 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Ocular melanoma is the leading intraocular malignancy. There is no effective treatment for metastatic ocular melanoma. We sought a treatment targeting the tumor microenvironment as well as the tumor cells. Methods: Migration of HUVEC cells, the ability of HUVEC cells to form tubes, and proliferative capacity of a human ocular melanoma cell line were tested in the presence of lenalidomide and sorafenib alone and in combination. The compds. were also tested in a rat aortic ring assay and were tested in a highly aggressive human ocular melanoma xenograft model. Results: Lenalidomide and Sorafenib inhibit HUVEC ability to migrate and form tubes and when used in combination the inhibition is increased. The agents alone and in combination inhibit outgrowth in the rat aortic ring model. The combination of the agents improved the inhibition over either single agent. In a xenograft model, combination therapy inhibited tumor growth over inhibition by single agent alone in a significant fashion ($p<0.004$: lenalidomide and $p<0.0035$: sorafenib). Furthermore, spontaneous lung metastasis development was completely inhibited in the combination treated animals. Sixty percent of vehicle treated animals developed lung metastases compared to 50% of lenalidomide treated animals, and 33% of sorafenib treated animals. Conclusions: Lenalidomide and sorafenib are effective at targeting endothelial cells, inhibiting growth of ocular melanoma cells and can inhibit growth of tumors in a xenograft model as well as inhibit development of metastases. Combining these agents works in an additive to synergistic way to inhibit the growth of tumors and development of metastases.

Answer 3:

Bibliographic Information

Immunomodulatory Drug CC-5013 or CC-4047 and Rituximab Enhance Antitumor Activity in a Severe Combined Immunodeficient Mouse Lymphoma Model. Hernandez-Ilizaliturri, Francisco J.; Reddy, Nishitha; Holkova, Beata; Ottman, Edris; Czuczman, Myron S. Department of Medicine, State University of New York at Buffalo, Buffalo, NY, USA. Clinical Cancer Research (2005), 11(16), 5984-5992. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:63981 AN 2005:864117 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New thalidomide derivs. CC-5013 and CC-4047 (immunomodulatory drugs, IMiD) are up to 10,000 times more potent than Thalidomide. The biol. effects of IMiDs are presumed to be mediated by (a) activation of some components of the innate [natural killer (NK) cells] or adoptive immune system (T cells), (b) modification of cytokine microenvironment in the tumor bed, or by (c) inhibition of angiogenesis. In this article, we tested an innovative combination strategy involving rituximab and IMiDs in aggressive lymphoma cell lines and human lymphoma xenografts. Treatment of non-Hodgkin's lymphoma cells with CC-5013 resulted in a 40% to 70% growth inhibition when compared with controls ($P < 0.05$). Exposure of lymphoma cells to CC-4047 resulted in a lesser degree of growth inhibition. Induction of apoptosis was shown in 10% to 26% of lymphoma cells 24 h following exposure to either IMiD. In vivo studies in severe combined immunodeficient mice showed synergistic activity between CC-4047 (and to a lesser degree, CC-5013) plus rituximab. Animals treated with the CC-4047/rituximab combination had a median survival of 74 days ($P = 0.0012$) compared with 58 days ($P = 0.167$) in CC-5013/rituximab-treated animals compared with 45 days in rituximab monotherapy-treated animals. The synergistic effect between IMiDs and rituximab in our mouse model was attributed to NK cell expansion. The enhancement of rituximab activity by IMiDs was abrogated by in vivo depletion of NK cells. Augmenting NK cell function by CC-4047 or CC-5013 exposure may increase the antitumor effects of rituximab against B-cell lymphomas and warrants further exploration in the context of a clin. trial.

Answer 4:

Bibliographic Information

The insulin-like growth factor-I receptor inhibitor NVP-AEW541 provokes cell cycle arrest and apoptosis in multiple myeloma cells. Maiso Patricia; Ocio Enrique M; Garayoa Mercedes; Montero Juan C; Hofmann Francesco; Garcia-Echeverria Carlos; Zimmermann Johann; Pandiella Atanasio; San Miguel Jesus F Centro de Investigacion del Cancer, CSIC-Universidad de Salamanca, Spain British journal of haematology (2008), 141(4), 470-82. Journal code: 0372544. E-ISSN:1365-2141. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18341634 AN 2008258491 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Multiple myeloma (MM) is a B-cell malignancy characterized by accumulation of monoclonal plasma cells in the bone marrow (BM). Despite recent advances in the treatment, MM represents an incurable disease for which development of new therapies is required. We report the antimyeloma effect of NVP-AEW541, a small molecule that belongs to the pyrrolo[2,3-d]pyrimidine class, identified as a selective inhibitor of the insulin-like growth factor-I receptor (IGF-IR) in vitro kinase activity. NVP-AEW541 had a potent cytotoxic effect on fresh cells and in a murine MM model. NVP-AEW541 partially abrogated the proliferative advantage conferred by the coculture with BM stromal cells and the presence of growth factors produced by the BM microenvironment. In addition, NVP-AEW541 potentiated the action of drugs, such as bortezomib, lenalidomide, dexamethasone or melphalan. Moreover the triple combination of NVP-AEW541, dexamethasone and bortezomib resulted in a significant increase in growth inhibition. Mechanistic studies indicated that NVP-AEW541 provoked a marked cell cycle blockade accompanied by pRb downregulation. Interestingly, NVP-AEW541 increased the levels of p27 associated with a reduction in the CDK2 activity. Finally, NVP-AEW541 induced cell death through caspase-dependent and -independent mechanisms. All these data, suggest the potential effect of IGF-IR kinase inhibitors as therapeutic agents for MM patients.

Answer 5:

Bibliographic Information

Targeting MEK induces myeloma-cell cytotoxicity and inhibits osteoclastogenesis. Tai Yu-Tzu; Fulciniti Mariateresa; Hideshima Teru; Song Weihua; Leiba Merav; Li Xian-Feng; Rumizen Matthew; Burger Peter; Morrison Aileen; Podar Klaus; Chauhan Dharminder; Tassone Pierfrancesco; Richardson Paul; Munshi Nikhil C; Ghobrial Irene M; Anderson Kenneth C The Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA. yu-tzu_tai@dfci.harvard.edu Blood (2007), 110(5), 1656-63. Journal code: 7603509. ISSN:0006-4971. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) written in English. PubMed ID 17510321 AN 2007491356 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Activation of the extracellular signal-regulated kinase1/2 (ERK1/2) signaling cascade mediates human multiple myeloma (MM) growth and survival triggered by cytokines and adhesion to bone marrow stromal cells (BMSCs). Here, we examined the effect of AZD6244 (ARRY-142886), a novel and specific MEK1/2 inhibitor, on human MM cell growth in the bone marrow (BM) milieu. AZD6244 blocks constitutive and cytokine-stimulated ERK1/2 phosphorylation and inhibits proliferation and survival of human MM cell lines and patient MM cells, regardless of sensitivity to conventional chemotherapy. Importantly, AZD6244 (200 nM) induces apoptosis in patient MM cells, even in the presence of exogenous interleukin-6 or BMSCs associated with triggering of caspase 3 activity. AZD6244 sensitizes MM cells to both conventional (dexamethasone) and novel (perifosine, lenalidomide, and bortezomib) therapies. AZD6244 down-regulates the expression/secretion of osteoclast (OC)-activating factors from MM cells and inhibits in vitro differentiation of MM patient PBMCs to OCs induced by ligand for receptor activator of NF-kappaB (RANKL) and macrophage-colony stimulating factor (M-CSF). Finally, AZD6244 inhibits tumor growth and prolongs survival in vivo in a human plasmacytoma xenograft model. Taken together, these results show that AZD6244 targets both MM cells and OCs in the BM microenvironment, providing the preclinical framework for clinical trials to improve patient outcome in MM.

Answer 6:

Bibliographic Information

Targeting PKC in multiple myeloma: in vitro and in vivo effects of the novel, orally available small-molecule inhibitor enzastaurin (LY317615.HCl). Podar Klaus; Raab Marc S; Zhang Jing; McMillin Douglas; Breitkreutz Iris; Tai Yu-Tzu; Lin Boris K; Munshi Nikhil; Hideshima Teru; Chauhan Dharminder; Anderson Kenneth C Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA. klaus_podar@dfci.harvard.edu Blood (2007), 109(4), 1669-77. Journal code: 7603509. ISSN:0006-4971. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17023575 AN 2007083114 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In multiple myeloma (MM) protein kinase C (PKC) signaling pathways have been implicated in cell proliferation, survival, and migration. Here we investigated the novel, orally available PKC-inhibitor enzastaurin for its anti-MM activity. Enzastaurin specifically inhibits phorbol ester-induced activation of PKC isoforms, as well as phosphorylation of downstream signaling molecules MARCKS and PKCmu. Importantly, it also inhibits PKC activation triggered by growth factors and cytokines secreted by bone marrow stromal cells (BMSCs), costimulation with fibronectin, vascular endothelial growth factor (VEGF), or interleukin-6 (IL-6), as well as MM patient serum. Consequently, enzastaurin inhibits proliferation, survival, and migration of MM cell lines and MM cells isolated from multidrug-resistant patients and overcomes MM-cell growth triggered by binding to BMSCs and endothelial cells. Importantly, strong synergistic

cytotoxicity is observed when enzastaurin is combined with bortezomib and moderate synergistic or additive effects when combined with melphalan or lenalidomide. Finally, tumor growth, survival, and angiogenesis are abrogated by enzastaurin in an in vivo xenograft model of human MM. Our results therefore demonstrate in vitro and in vivo efficacy of the orally available PKC inhibitor enzastaurin in MM and strongly support its clinical evaluation, alone or in combination therapies, to improve outcome in patients with MM.